PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 92/11046
A61M 1/16	A1	(43) International Publication Date:	9 July 1992 (09.07.92)

(21) International Application Number: PCT/US90/07480

(22) International Filing Date: 18 December 1990 (18.12.90)

(71) Applicant: THE BOARD OF REGENTS OF THE UNIVERSITY OF WASHINGTON [US/US]; 3755 University Way N.E., Seattle, WA 98105 (US).

(72) Inventors: AHMAD, Suhail ; 10301 40th Avenue N.E., Seattle, WA 98125 (US). COLE, James, J. ; 19512 Jordan Road, Arlington, WA 98223 (US). JENSEN, William ; P.O. Box 75262, Seattle, WA 98125 (US).

(74) Agents: SEED, Richard, W. et al.; Seed and Berry, 6300 Columbia Center, Seattle, WA 98104-7092 (US).

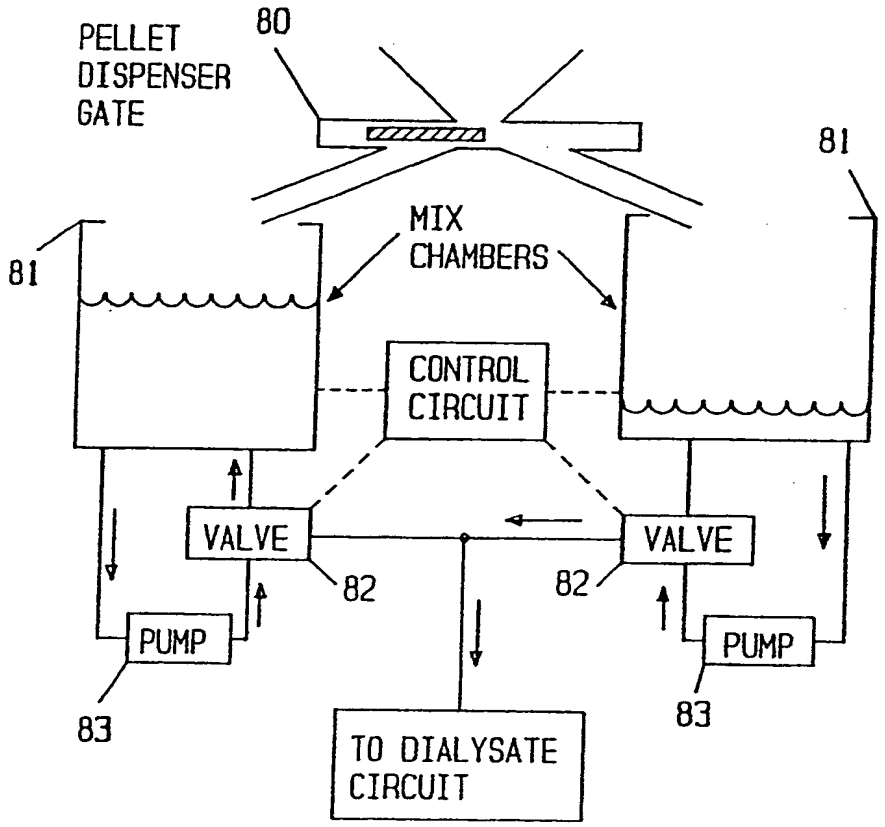
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
With amended claims.

(54) Title: DIALYSATE PRODUCTION SYSTEM WITH DIALYSATE PELLETS

(57) Abstract

Dry chemical pellets containing an acid, base, and salt, have the necessary chemicals to form a dialysate when mixed with a predetermined amount of water stored in mixing tanks from which the dialysate can be circulated to a hemodialysis circuit. The pellets can be varied in composition and dispensed in a prescribed order to vary the dialysate in accordance with the patient's needs.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE•	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

Description

DIALYSATE PRODUCTION SYSTEM WITH DIALYSATE PELLETS

Technical Field

The present invention relates to hemodialysis systems, and more particularly, to an improved system for supplying dialysates.

Background of the Invention

Hemodialysis treatment is employed as a therapeutic measure when a patient's kidneys no longer perform their blood purifying function because of disease or traumatic removal. Kidney failure results in the accumulation of toxic waste in the patient's blood and eventual death from uremic poisoning, unless the waste material is removed by some artificial means. In hemodialysis of the type to which the present invention relates, the patient's blood is circulated from the patient in a closed blood circuit by a pump to one side of a membrane contained within a hemodialyzer (i.e., artificial kidney). The membrane has pores of microscopic size through which waste products from the blood pass. The pores are, however, too small to permit blood cells and proteins to leave the body. A dialysis fluid (dialysate) is circulated on the other side of the hemodialyzer membrane to remove the waste products. The dialyzed blood is returned to the patient.

Commonly the dialysate for hemodialysis systems is supplied as a liquid concentrate in containers from which it is blended and diluted with sterile water by the use of proportional pumping systems.

Brief Description of the Invention

The present invention provides an on-site dialysate production system for supplying dialysate directly to a hemodialysis system by utilizing dry chemical pellets or tablets, wherein the pellet or tablet contains an acid or acids, a base or bases, and salts, with the proviso that the acid component be separated from the base component. The pellets are added to mixing chambers containing treated water to form the dialysate. The mixed dialysate from the chambers flows into the dialysate circuit through the hemodialyzer and/or hemofilter. Preferably, the acid component is citric acid, and this forms an effervescence upon contact with water and other chemicals to facilitate the solution of the dry chemical into the dialysate and maintains a pH below 7.4. Moreover, the more acid pH prevents calcium carbonate from forming an insoluble precipitate in the aqueous solution.

Brief Description of the Drawings

Figure 1 is a schematic of the main components in a traditional hemodialysis system.

Figure 2 is a schematic of a dialysate production system embodying the present invention.

Detailed Description of the Invention

Referring to Figure 1, an "arterial" line runs from the patient to a blood pump and then to one side of the membrane in the hemodialyzer. The blood then flows to a drip chamber in the "venous" line and back into the patient. This forms the blood circuit. Conventionally, the dialysate circuit has been formed by mixing liquid dialysate concentrate with sterile water and passing the resulting dialysate on the other side of the hemodialyzer membrane and then continuing out to waste.

Referring to Figure 2 in the dialysate production system of this invention, dry chemical pellets

or tablets in a hopper or magazine are dropped, or otherwise fed, into a pellet dispenser gate (80) and then added to one of two mixing chambers (81) containing a predetermined amount of sterile water. Preferably, a pump (83) circulates the water in the mix chamber to dissolve the pellet, and form a dialysate solution. Citric acid in the pellet regulates the pH of the dialysate to pH 7.4 or below to prevent calcium carbonate precipitate from forming. A valve (82) controls the addition of the dialysate in the mix chamber to the dialysate circuit. This system eliminates the need for use of a concentrate proportioning pump in prior art systems.

In accordance with the present invention, dry chemicals are formed into the pellets in premeasured amounts. Each pellet contains an acid, base, and salt in dry form. Preferably, the acid is citric acid and is separated from the base and salt. Preferably, the pellets are formed and stored under low humidity conditions. The pelletized dry chemicals are capable of forming dialysates with either acetate-based or bicarbonate-based dialysates without equipment conversion. Preferably, the salt forms a barrier layer between the acid and the base in the pellet.

The dry chemicals suitable for use in the pellets include salts comprising an anion and a cation, wherein the anions are selected from the group consisting of bicarbonate, citrate, chloride, acetate, lactate, and combinations thereof; and wherein the cations are selected from the group consisting of sodium, potassium, magnesium, calcium, and combinations thereof. Additional organic dry chemicals suitable for use as salts include dextrose and urea. Useful acids include citric acid, lactic acid, ascorbic acid and acetic acid. Typical bases include bicarbonate, carbonate, lactate and citrate. Preferably, sodium, potassium, calcium, and magnesium are the cations. A suitable dry dialysate composition in pellet form that can be mixed with one liter of water to form one liter of

dialysate comprises from about 130 to about 150 mEq Na, from 0 to about 4.0 mEq of K, from about 2.0 to 3.5 of mEq Ca, from 0 to about 1.5 mEq Mg, from about 25 to about 45 mEq bicarbonate, from 0 to about 2 g/L glucose, and from about 90 to about 120 mEq chloride ion. Acetate or lactate can be substituted for bicarbonate at the same concentration range. Preferably, citric acid is used at a concentration from about 2 to 12 mEq to maintain an acid pH of the dialysate.

Each mix chamber 81 can contain, for example, from about 2 to about 10 liters of dialysate. Each dialysate chamber volume can be prepared by mixing an appropriate volume of water with a single pellet. The valves 83 located in the pump circuit can switch a mix chamber into a dialysate reservoir to pump dialysate through the dialysate circuit to the hemodialyzer and out to waste. The second mix chamber can be preparing the next reservoir of dialysate for use when the first mix chamber becomes empty. Hence, preferably there are at least two mixing chambers 81.

The use of citric acid in conjunction with conventional dialysate chemicals produces a mixture which will dissolve quickly and completely in the time required by the system. The resulting citrate load is well tolerated, and causes no disturbance of the blood calcium level. Construction of the pellet, such that the more acid components dissolve first, maintains the pH of the solution below the level of 7.40 at all times. This chemical environment prevents the formation of insoluble precipitates, especially calcium salts.

The pellets can be loaded in prescribed order in a suitable pellet dispenser means controlled by the pellet dispenser gate 80 to change the ion gradient of the dialysate during the treatment process to better suit the individual patient's treatment needs.

It is possible to attach a bar code to the pellet and an optical scanner in the means for adding

pellets to the mixing chambers to ensure proper gradient formation and to allow the mixing system to adjust monitoring according to pellet composition. The pellets can be preloaded in magazines or casettes.

As previously indicated, the utilization of discrete tables or pellets makes it possible to easily change the chemical makeup of the dialysate during treatment in accordance with changing requirements of the individual patient. For example, Raja et al., "Role of Varying Dialysate Sodium and Bicarbonate in the Improvement of Dialysis Vascular Stability," Prog. Art. Organs, Nose et al. (eds.), ISAO Press, Cleveland, 1985, pp. 237-39 [Raja et al. I], and Raja et al., "Sequential Changes in Dialysate Sodium (DNa) During Hemodialysis," Trans. Am. Soc. Artif. Intern. Organs 29:649-651, 1983 [Raja et al. II] describe several schemes to vary dialysate ion concentrations during treatment. The ability to introduce, in prescribed order, pellets with different chemical makeup into the mixing chambers makes possible the timed adjustment in individual dialysate ion concentrations during dialysis treatment in accordance with the prescription of the managing physician.

For example, the dialysate sodium concentration can be progressively changed from 150 to 135 mEq/L in decrements of 1 or 2 mEq/L during the course of treatment. At the same time, the bicarbonate concentration might be altered from 20 to 35 mEq/L in 5 mEq/L increments during the first 3 hours of the procedure. The dialysate chemical composition can be flexibly changed every few minutes, as each new pellet is introduced, to produce optimal treatment results according to the defined needs of the individual patient. It will be appreciated that the system can be automated and programmed to control the feeding of the pellets and delivery of the dialysate to the dialysis circuit.

Another example of the benefit of being able to vary the dialysate ion concentration during treatment is

to control the rate of osmolar change during dialysis. Several treatment-related symptoms during dialysis have been shown to be related to osmolar decline, and the reduction or blunting in this decline can also reduce treatment symptoms, thus improving the quality of dialysis. One way to achieve this goal is to use sodium modeling. The sodium concentration in the dialysate is increased in the early phase of dialysis and then is slowly reduced to lower concentrations, thus blunting the rate of decline of blood osmolarity. Sodium modeling can only be accomplished, at present, with additional equipment added to a basic dialysis system, and then the procedure is nonselective, altering both sodium and other ions proportionally. The present invention achieves sodium modeling by loading dry dialysate pellets with higher sodium concentrations for the early part of dialysis treatment and then gradually using pellets with lower sodium concentrations throughout the remainder of the treatment. Similarly, other osmolar agents, for example urea, can be added.

In present dialysis systems, changing the sodium concentration also proportionally alters the concentrations of other constituents, such as calcium and magnesium. Because individual pellets can be introduced at frequent intervals with the inventive system, the concentrations of all ionic species, except those whose change is desired, can be held constant.

It will be appreciated that, although the invention has been described with respect to dialysate for hemodialysis, it is also applicable to supplying dialysate for peritoneal dialysis, in which case greater quantities of glucose can be used, and the dialysate circuit connects to the patient rather than to the hemodialyzer.

Claims

1. A dialysate production system comprising:

a plurality of dry dialysate pellets;

a mixing tank;

a gating device arranged and adapted to control the addition of dry dialysate pellets to said mixing tank;

a water source;

a means for circulating a fixed volume of water from said water source to the mixing tank to dissolve a dry dialysate pellet therein to form dialysate in the mixing tank; and

circulating means for circulating said dialysate from the mixing tank to a use site.

2. The dialysate production system of claim 1 wherein there is a second mixing tank operatively associated with said gating device, water source and circulating means whereby dialysate may be alternately circulated from said tanks.

3. The dialysate production system of claim 1 wherein the dry dialysate pellet comprises an acid, a base and a salt in layers.

4. The dialysate production system of claim 3 wherein the acid is citric acid.

5. The dialysate production system of claim 3 wherein the salt comprises an anion and a cation.

6. The dialysate production system of claim 5 wherein the anion is selected from the group consisting of bicarbonate, lactate, citrate, chloride, acetate and combinations thereof.

7. The dialysate production system of claim 5 wherein the cation is selected from the group consisting of sodium, potassium, magnesium, calcium and combinations thereof.

8. The dialysate production system of claim 3 wherein said salt is a layer between said acid and base.

9. The dialysate production system of claim 1, in which said use site is a hemodialyzer.

10. A dry dialysate composition comprising a pellet having a plurality of respective layers of an acid and a base and a salt, wherein the acid will dissolve first in an aqueous solution and the base will dissolve after solution of the acid.

11. A dry dialysate composition according to claim 10, in which said layers are separated from one another.

12. The dry dialysate composition of claim 10, wherein the acid is citric acid.

13. A dry dialysate composition according to claim 10, in which said salt is a layer between said acid and base.

14. A dry dialysate composition that, upon mixing with water, forms a dialysate comprising:

from about 130 to about 150 mEq/L of sodium ion;

from about 0 to about 4.0 mEq/L of potassium;

from about 2.0 to about 3.5 of mEq/L of calcium ion;

from about 0 to about 1.5 mEq/L of magnesium ion;

from about 25 to about 45 mEq/L of bicarbonate ion, acetate, lactate or combinations thereof;

from about 0 to about 2.0 g/L glucose; and

from about 90 to about 120 mEq/L of chloride ion.

15. The dry dialysate composition of claim 13 further comprising from about 2 to about 12 mEq/L of citric acid whereby the citric acid maintains an acid pH of the dialysate.

16. A dry dialysate composition in a pellet or tablet form comprising an acid, a base and a salt wherein the acid is selected from the group consisting of citric acid, lactic acid, ascorbic acid, acetic acid and combinations thereof, and wherein the base is selected from the group consisting of bicarbonate, carbonate, lactate, citrate and combinations thereof.

AMENDED CLAIMS

[received by the International Bureau on 20 April 1992 (20.04.92); original claims 3,4,8,9,11,13 and 15 cancelled; new claims 3 and 7 added; claims 1,2,5,6,7,10,12 and 16 amended and renumbered as claims 8,9,10,11,12,1,2, and 5 (3 pages)]

1. A dry dialysate composition comprising a pellet with a plurality of separated layers of an acid, bicarbonate and a salt, wherein the acid will dissolve first in an aqueous solution and the bicarbonate will dissolve after solution of the acid.

2. The dry dialysate composition of claim 1 wherein the acid is citric acid.

3. The dry dialysate composition of claim 1 wherein, upon dissolving in water, the pH remains below 7.4.

4. A dry dialysate composition that, upon mixing with water, forms a dialysate comprising:

from about 130 to about 150 mEq/L of sodium ion;

from about 0 to about 4.0 mEq/L of potassium ion;

from about 2.0 to about 3.5 mEq/L of calcium ion;

from about 0 to about 1.5 mEq/L of magnesium ion;

from about 25 to about 45 mEq/L of bicarbonate ion, acetate, lactate or combinations thereof;

from about 0 to about 2.0% glucose;

from about 90 to about 120 mEq/L of chloride ion; and

from about 2 to about 12 mEq/L of citric acid.

5. A dry dialysate composition in a pellet or tablet form comprising an acid, a base and a salt wherein the acid is selected from the group consisting of citric acid, lactic acid, ascorbic acid, acetic acid and combinations thereof and wherein the base is selected from the group consisting of bicarbonate, carbonate, lactate, citrate and combinations thereof.

6. A dry dialysate composition that, upon mixing with water, forms a dialysate comprising:

from about 130 to about 150 mEq/L of sodium ion;

from about 2.0 to about 3.5 mEq/L of calcium ion;

from about 25 to about 45 mEq/L of bicarbonate ion, acetate, lactate or combinations thereof;

from about 90 to about 120 mEq/L of chloride ion; and

from about 2 to about 12 mEq/L of citric acid.

7. A dry dialysate composition comprising an acid, a base and a salt wherein the acid is selected from the group consisting of citric acid, ascorbic acid and combinations thereof and wherein the base is selected from the group consisting of bicarbonate, carbonate, lactate, citrate and combinations thereof.

8. A dialysate production system comprising:

a plurality of dry dialysate compositions according to any one of claims 1, 2, 3, 4, 5, 6 or 7;

a mixing tank;

a gating device arranged and adapted to control the addition of dry dialysate pellets to said mixing tank;

a water source;

a means for circulating a fixed volume of water from said water source to the mixing tank to dissolve a dry dialysate pellet therein to form dialysate in the mixing tank; and

circulating means for circulating said dialysate from the mixing tank to a hemodialyzer.

9. The dialysate production system of claim 8 wherein there is a second mixing tank operatively associated with said gating device, water source and circulating means whereby dialysate may be alternately circulated from said tanks.

10. The dialysate production system of claim 8 wherein the salt comprises an anion and a cation.

11. The dialysate production system of claim 10 wherein the anion is selected from the group consisting of bicarbonate, lactate, citrate, chloride, acetate and combinations thereof.

12. The dialysate production system of claim 10 wherein the cation is selected from the group consisting of sodium, potassium, magnesium, calcium and combinations thereof.

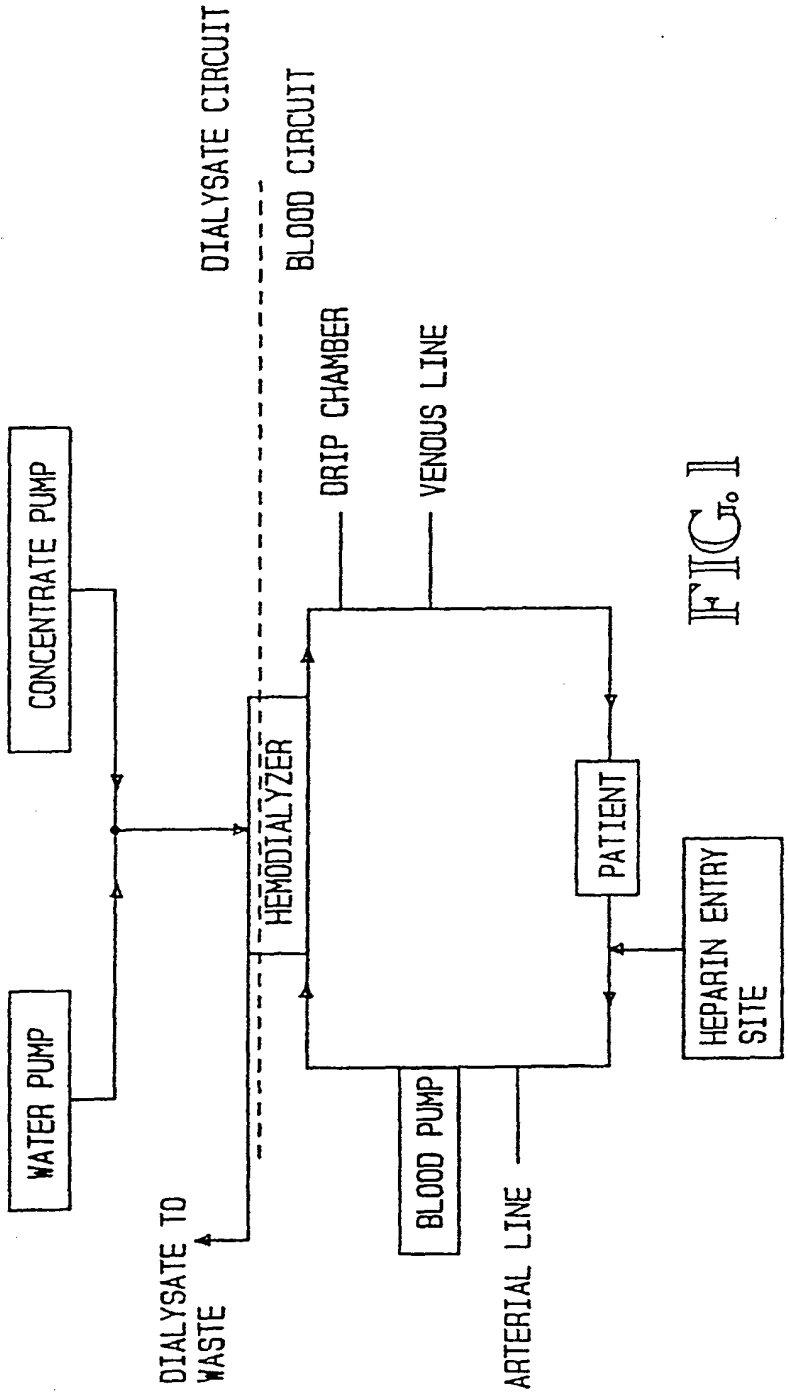

DIALYSATE CIRCUIT
BLOOD CIRCUIT
DRIP CHAMBER
VENOUS LINE
CONCENTRATE PUMP
WATER PUMP
HEMODIALYZER
PATIENT
HEPARIN ENTRY SITE
DIALYSATE TO WASTE
BLOOD PUMP
ARTERIAL LINE

FIG. 1

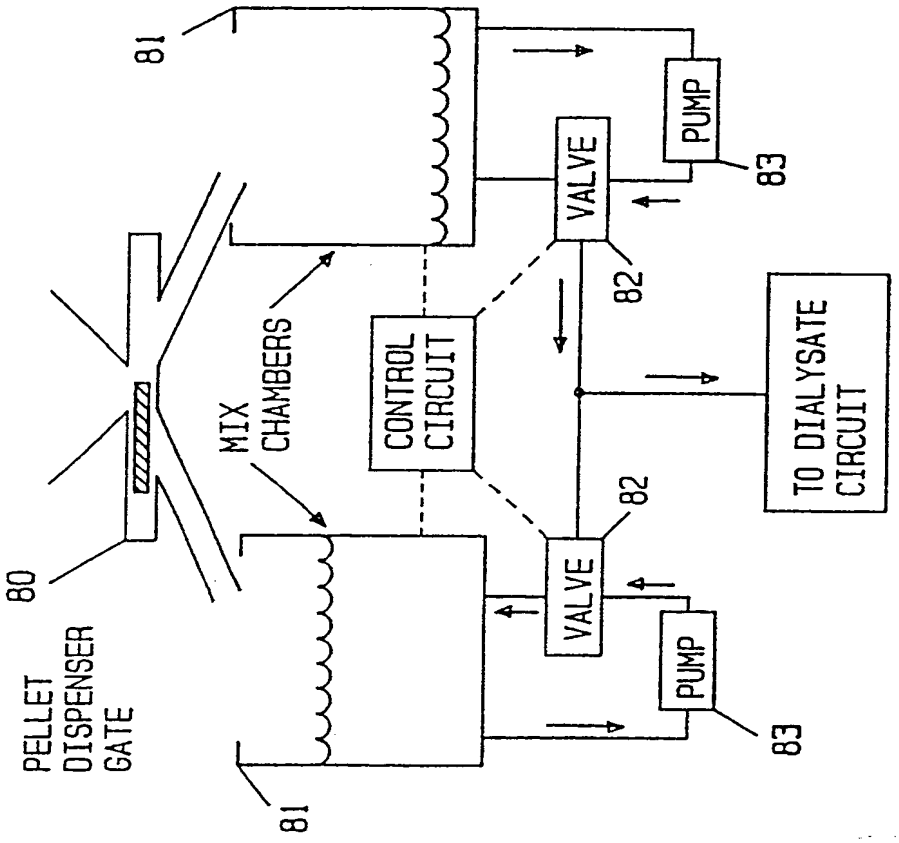

81
PUMP
83
VALVE
82
CONTROL CIRCUIT
MIX CHAMBERS
TO DIALYSATE CIRCUIT
82
VALVE
PUMP
83
80
PELLET DISPENSER GATE
81

FIG. 2

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent [illegible]cation (IPC) or to both National Classification and IP[illegible]

Int.Cl.5 [illegible]61 M 1/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0034916 (P. VELTMAN) 2 September 1981, see page 6, line 21 - page 7, line 2; page 10, lines 5-24	1,10,16
A	US,A,4734198 (W. HARM et al.) 29 March 1988, see abstract; figures	1
A	FR,A,2569560 (S. GRANGE et al.) 7 March 1986, see the whole document	1
A	EP,A,0399918 (TERUMO) 28 November 1990, see page 3, lines 13-39	1,10,16

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14-08-1991	06. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Nicole De Bie

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. Claims 1-13,15,16
2. Claim 14

For further information please see form PCT/ISA/206 mailed on 25.09.19991.

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

1-13,15,16

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9007480
SA 43896

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 20/12/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0034916	02-09-81	US-A- 4756838	12-07-88
		AU-A- 6747081	27-08-81
		CA-A- 1167378	15-05-84
		JP-A- 56131515	15-10-81
		US-A- 4489535	25-12-84
US-A- 4734198	29-03-88	None	
FR-A- 2569560	07-03-86	None	
EP-A- 0399918	28-11-90	JP-A- 2311418	27-12-90
		JP-A- 2311419	27-12-90
		JP-A- 3038527	19-02-91
		AU-A- 5580390	29-11-90